INTERfering and Co-Evolving Prevention and Therapy (INTERCEPT)

Proposers Day

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Arlington, VA

INTERCEPT Agenda

- INTERCEPT Program Motivation and Overview
- INTERCEPT Program Objectives
- INTERCEPT Technical Areas
- Timeline and Milestones
- Proposal Guidance

Disclaimer:

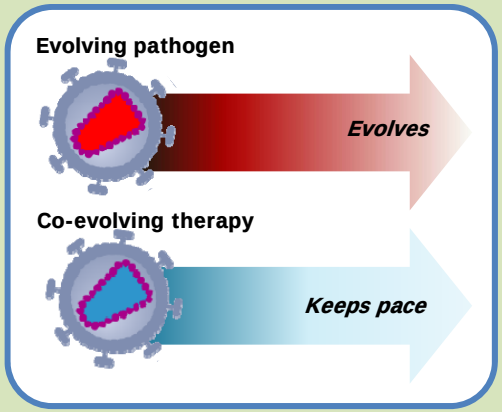
In the event of a disagreement between the contents of the BAA and the information in this briefing, please follow the BAA. No exceptions.

INTERCEPT Vision

Novel approach to combat viral diseases

Problem: Vaccines, antibiotics, small drugs are static; they treat pathogen as a fixed target at time of diagnosis

Human pathogens mutate and evolve; current therapies can't keep up with the moving targets

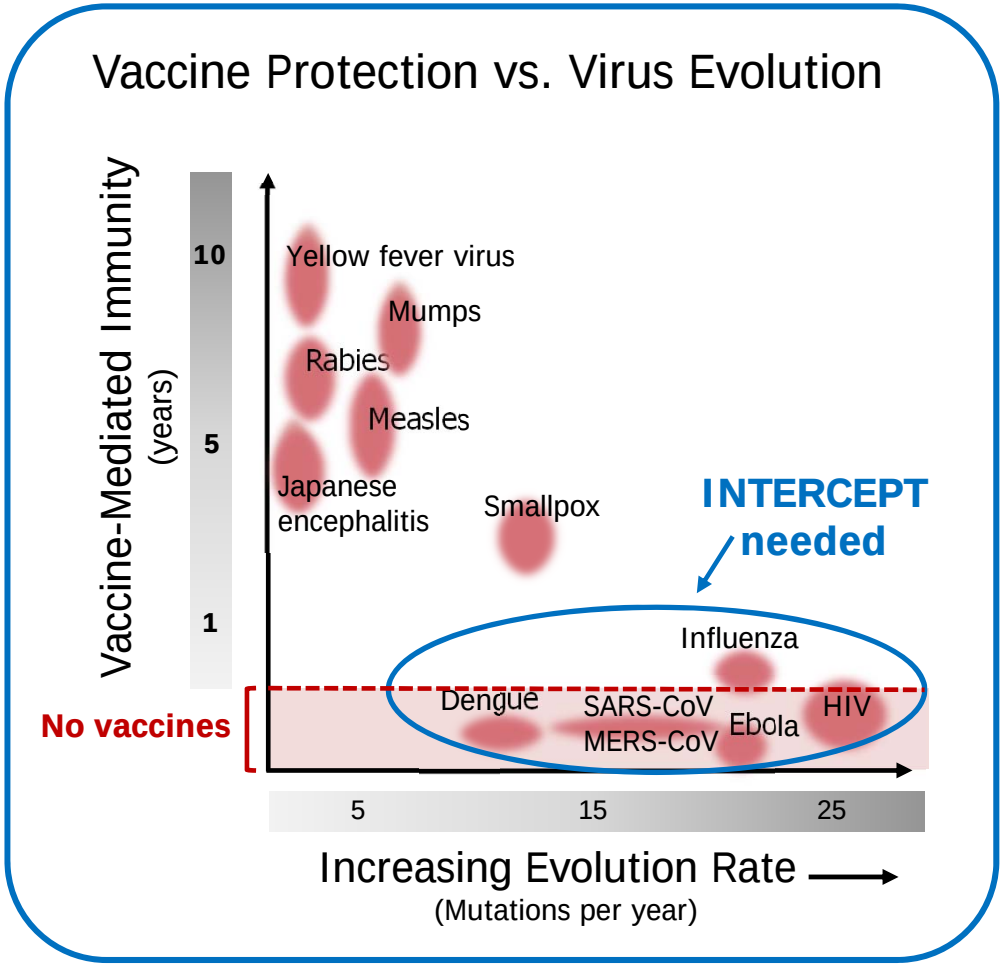


DARPA Approach:

- Use *evolution* to defeat *evolving* pathogens
- Develop *non-static* therapies that *track* and *keep pace* with fast-evolving targets

Goal: Develop co-evolving therapy platforms to protect the warfighter and the public against rapidly evolving viral pathogens and biothreats

Wait, what's the problem and why DARPA?



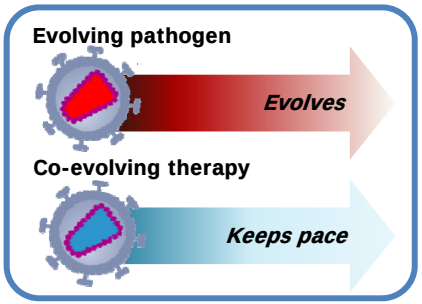
Challenges

- Fast-evolving virus biothreats
- Growing number of viruses with no vaccines or therapies
- Slow response time to new threats

Static therapeutics can't keep up

- Pathogen evolution leads to resistance, therapeutic obsolescence
- Drugs must undergo costly re-design and testing
- Health response teams have limited tools to combat new strains and biothreats

We need a new paradigm!

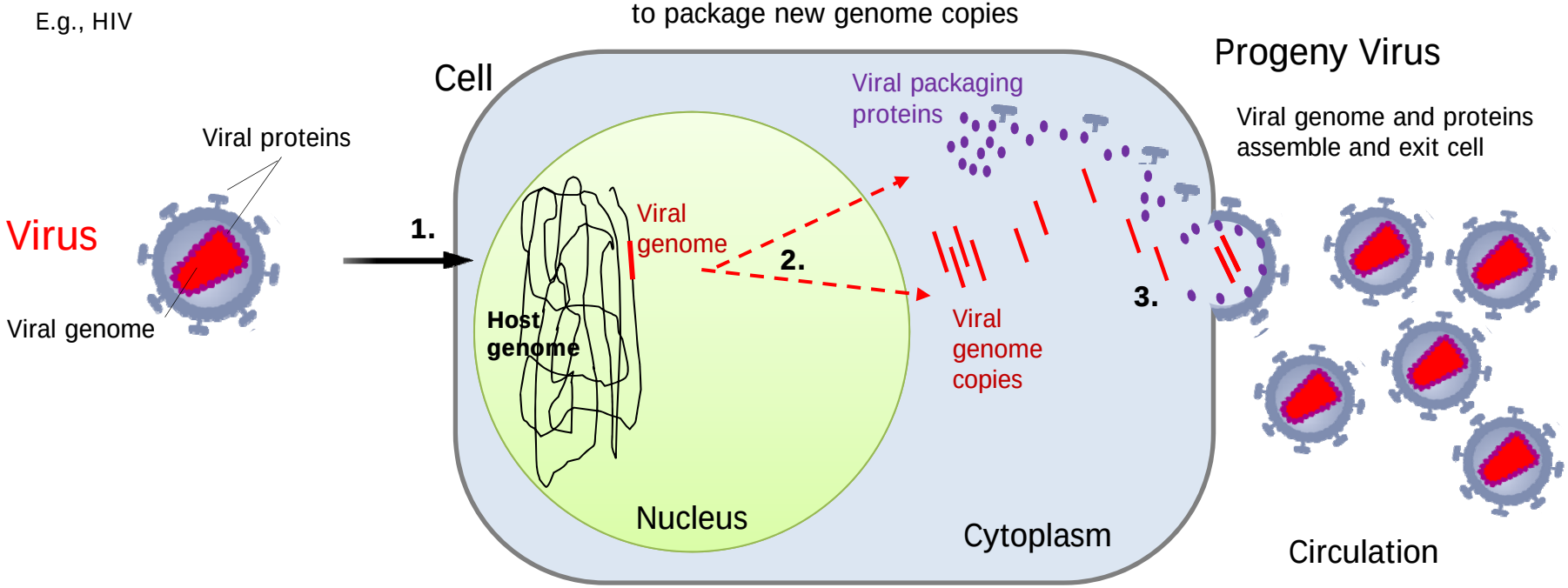


Viral infection of a host cell

- Virus hijacks the cell to amplify itself and egress to infect other cells

Viral genome

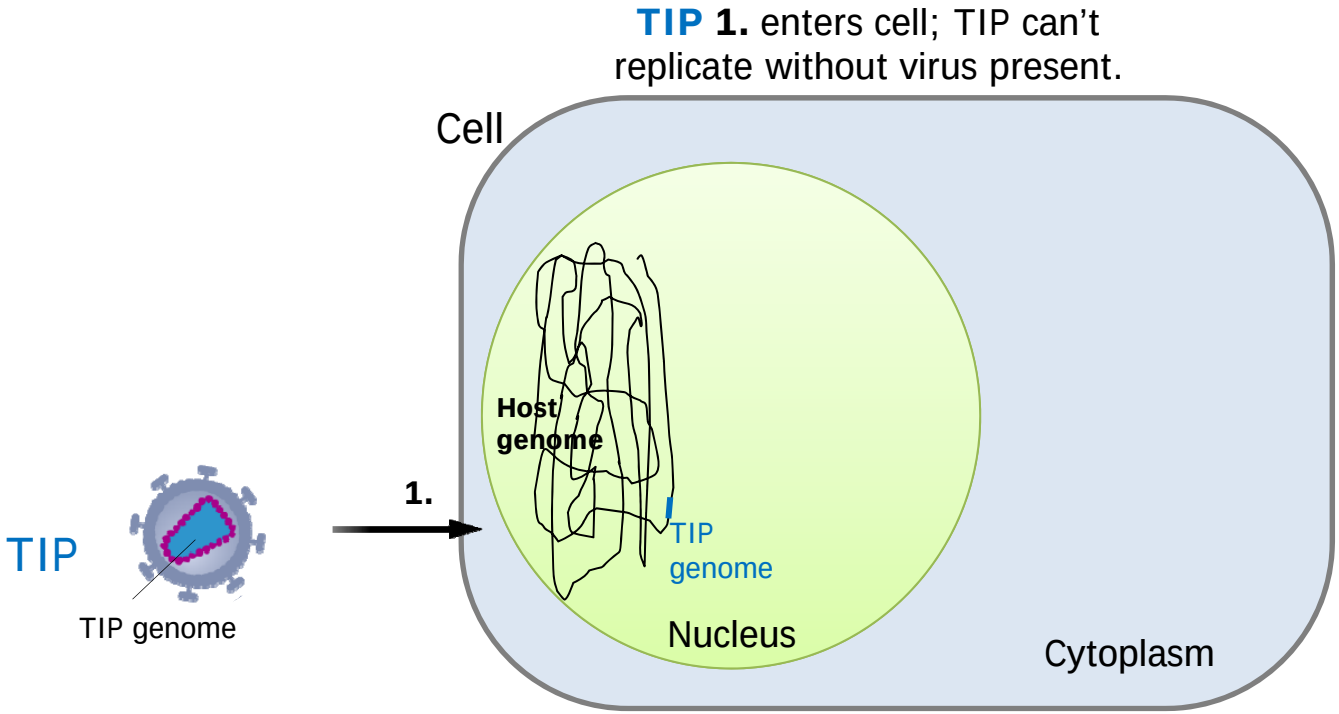
Virus **1.** enters cell; **2.** replicates its genome and produces viral proteins; **3.** uses proteins to package new genome copies



Therapeutic Interfering Particle (**TIP**)

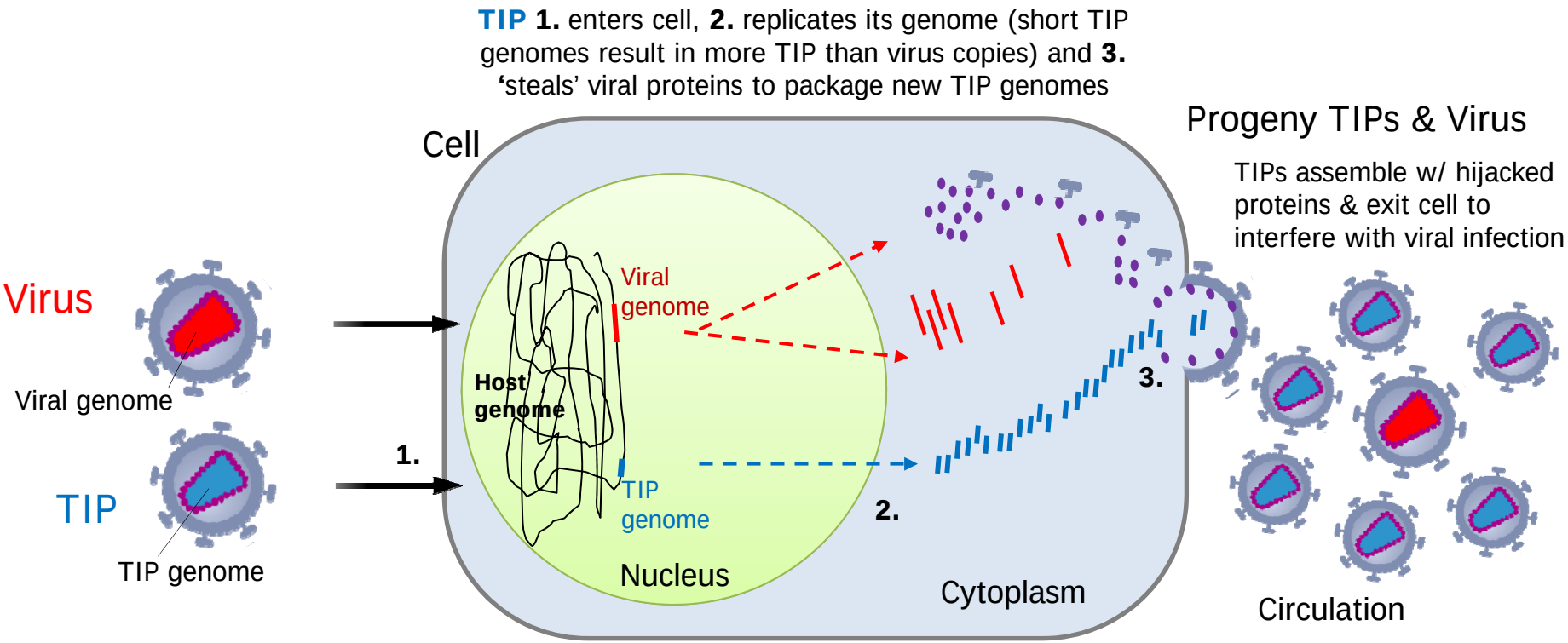
- TIPs are derived from virus *but* lack essential genes for replication
- TIPs are not active in the absence of virus

TIP genome – Truncated genome



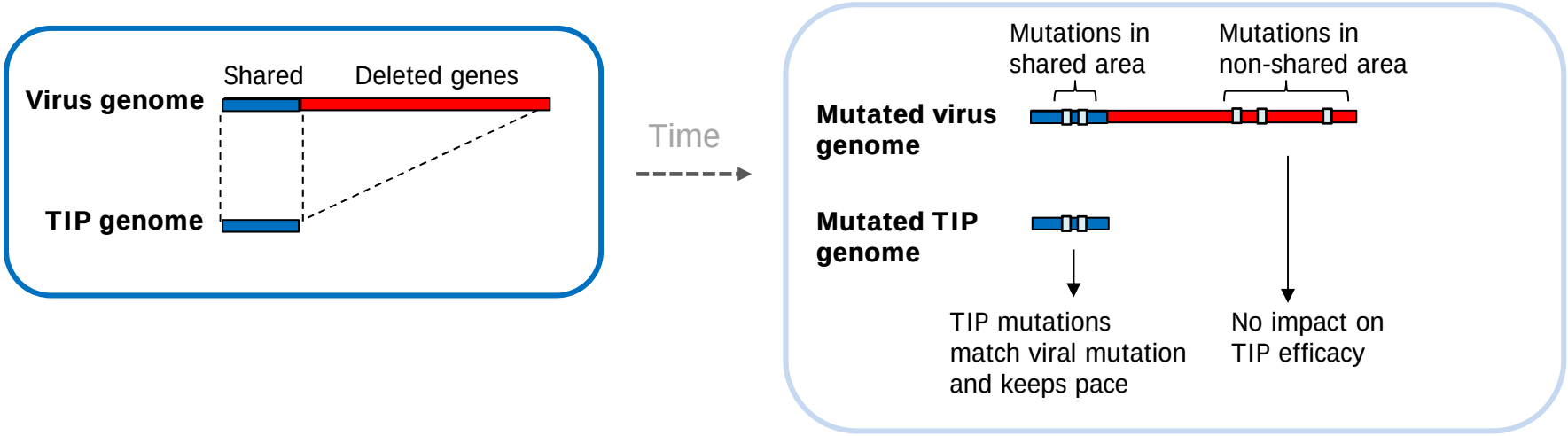
How TIP interferes with viral infection

- TIPs stoichiometrically out-compete virus for viral proteins, allowing TIPs to form and exit cell
- This results in reduced formation and release of virus that can infect other cells



Co-evolutionary dynamics:
TIPs keep pace with fast evolving viruses

TIP and full length virus both undergo mutations at similar rates;
Spectrum of virus and TIP variants coexist in host, each variant facing selection pressures.



During infection, virus accumulates mutations along its genome

TIP treatment is effective even if virus evolves:

- Mutations occurring in viral genes not shared with TIP have little impact on TIP efficacy
- To escape TIP, virus must undergo multiple mutations including mutations within genome region common to TIP; however, TIP can readily produce a matching mutation that enables it to keep pace with virus

Impact: TIPs as a general platform

Address diverse mechanisms of replication and transmission

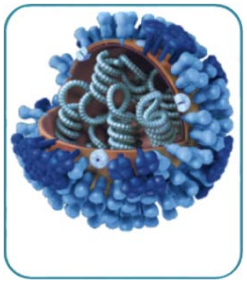
Develop TIP platform to address broad spectrum of fast evolving viral threats that lack or have weak vaccines & therapies

HIGH PRIORITY VIRAL PATHOGHENS			
Dengue	SARS-CoV	Ebola	JC virus
Zika	MERS-CoV	Crimean Congo HV	BK virus
Hantaviruses	Lassa	Lujo	Chapare
Nipah	Junin	Machupo	Guanarito
Hendra	Sabia	Caliciviruses	West Nile
Rift Valley Fever	St. Louis encephalitis	LaCrosse encephalitis	California encephalitis
Western equine encephalitis	Eastern equine encephalitis	Enterovirus 68	Enterovirus 71
Chikungunya	Hepatitis C	Herpes simplex	HIV
Japanese encephalitis	Venezuelan equine encephalitis	Influenza	Hepatitis E
Crimean Congo Hemorrhagic Fever	Marburg	Severe Fever with Thrombocytopenia Syndrome	Heartland
Omsk Hemorrhagic Fever	Alkhurma virus	Kyasanur Forest	Tickborne encephalitis complex flaviviruses

(http://www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/Pages/CatA.aspx)

INTERCEPT Technical Areas

Exploit emerging technologies for TIP development, optimization, testing

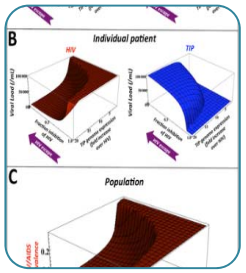


TA1: TIP development

- Design and generate TIP candidates that outcompete pathogen, cannot self-activate (obligate parasites)
- Screen & optimize initial TIPs for short term efficacy and toxicity *in vitro*

TA2: Co-evolution testing

- Build dynamic *in vitro* platforms for long-term co-evolutionary assessment in *in vivo*-like conditions
- Assess long term evolutionary safety and efficacy *in vitro* and *in vivo*

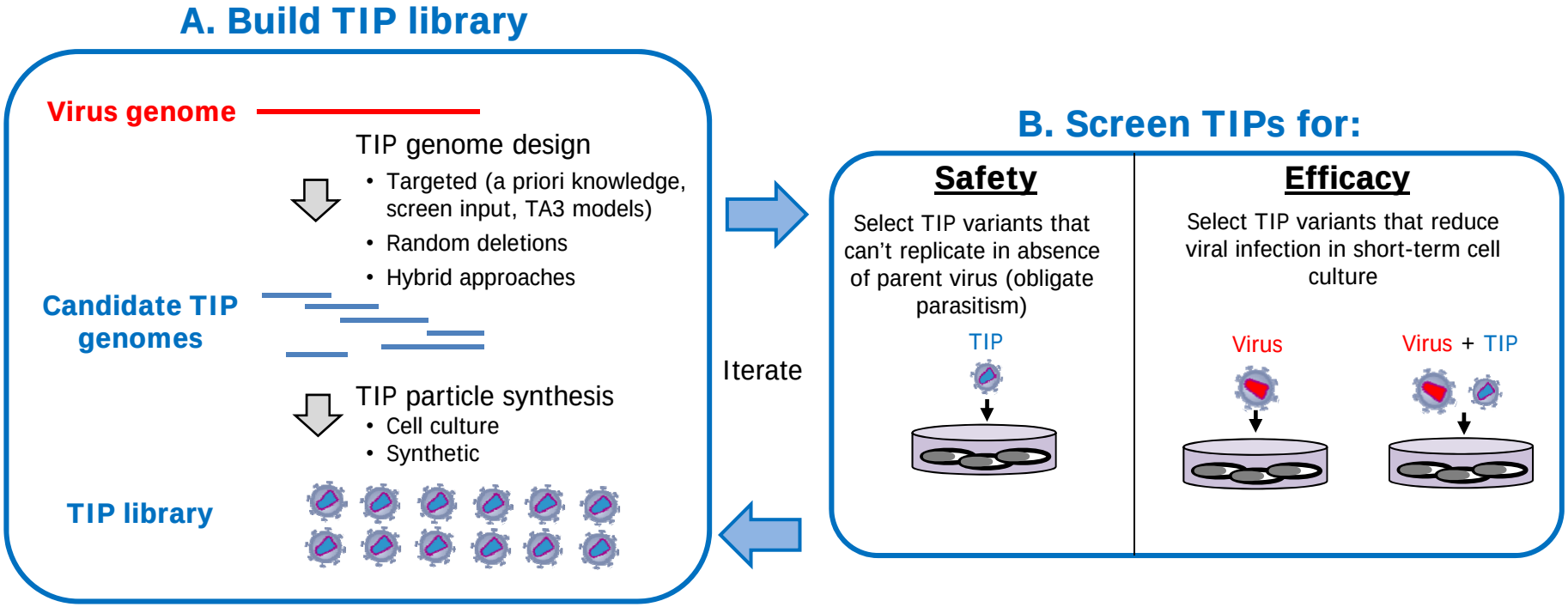


TA3: Modeling

- Develop *in-silico* modeling platform to inform TIP design
- Develop models of viral kinematics, safety, efficacy, and co-evolution at cell, host and population levels

TA1: TIP development

Objective: Engineer TIPs that stoichiometrically outcompete virus but are inactive/dormant in the absence of infection with the virus



Deliverables:

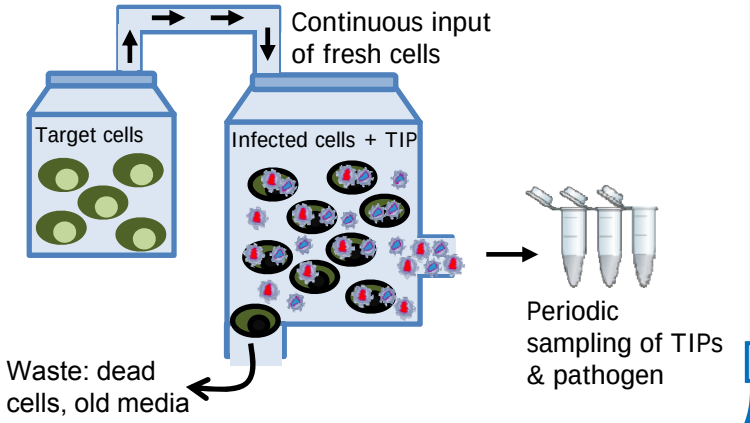
- Optimized TIPs screened for safety and efficacy reduce viral infection in short-term cell cultures

TA2: Co-evolution testing

Objective: Evaluate TIPs for long-term toxicity, efficacy and co-evolution

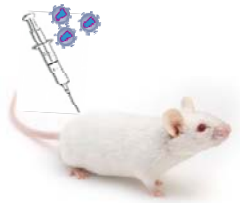
In vitro testing

Example: Develop continuous evolutionary bioreactors



In vivo testing

Animal models of infectious diseases



- Assess TIP dose, toxicity, efficacy, and co-evolution long-term in target organ and systemic
- Evaluate host immune response
- Transmission studies

- Periodic sequencing of TIP and pathogen genes to monitor pathogen-TIP mutations & co-evolution
- Quantify stable reduction of pathogen load long term

Deliverables:

- Long-term validation: co-evolution, safety, efficacy *in vitro* and/or *in vivo* for selected virus types

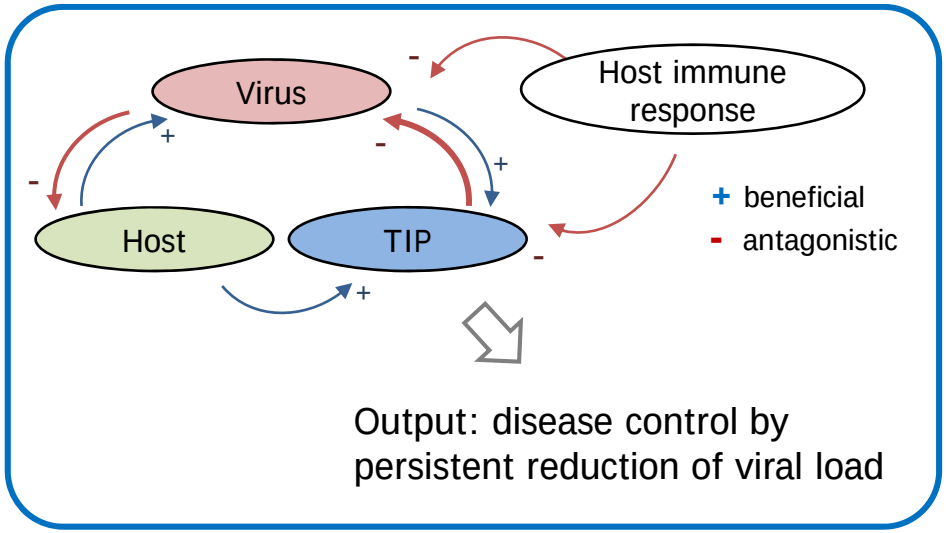
TA3: Modeling

Objective: Build *in silico* model that captures virus/TIP/host and population-level dynamics to support TIP design and platform development

Cell level:
- TIP and virus kinematics
- TIP optimization

Host level:
- TIP efficacy, safety, co-evolution with viral mutations and host immune response

Population level:
- TIP evolution, stability, transmission



Deliverables:
- *In silico* TIP-pathogen-host dynamics and co-evolution framework at cell-, host-, and population-level
- Predictive models for long-term TIP efficacy, safety, optimal design feeding back to TA1

Proposal guidance

Read the BAA carefully!

For all Technical Areas:

- Justify virus candidate/s selected for study
- Summarize key innovations, how your approach advances beyond current practice
- Back up your idea and technical approach (e.g. by theoretical arguments, models, past results, new data)
- Provide quantitative metrics feasible within the proposed timeline
- Summarize key expected outputs and deliverables

Proposal guidance continued

Proposers must address **one** of the following:

A. All three Technical Areas (TAs);
B. Both TA2 and TA3; *or*
C. TA3 – *Must identify collaborator/s to team to address TA2 before the end of the first year of contract*

Proposals that focus solely on Technical Area 1 or solely on Technical Area 2 will not be considered for funding.

Teaming

It is anticipated that teaming will be necessary to meet the goals of this program

Tips:

1. Listen to presenters during today's attendee presentation sessions, where attendees will briefly present their expertise and capabilities
2. Reach out to colleagues and collaborators

BAA Inbox and FAQ

- Direct all questions and communication to the BAA Inbox DARPA-BAA-16-35@darpa.mil

- BAA Inbox FAQ DARPA will post a consolidated FAQs on a regular basis
  - To access the posting go to:

http://www.darpa.mil/work-with-us/opportunities?tFilter=&oFilter=1&sort=date

Some advice

- Read the BAA, carefully –and respond accordingly.
  - Some instructions are specific –“required” and “must”
  - Most of the instructions are non-specific –you decide on what is the best possible science to support the objectives of the program
  - Be honest about risks and demonstrate thoughtful consideration for how to mitigate those risks.
  - Ask for clarification as needed. FAQs will be updated regularly.
  - Take advantage of today’s opportunities to meet potential teammates and ask questions

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